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AllergoOncology: IgE- and IgG_4-mediated immune mechanisms linking allergy with cancer and their translational implications

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Since the detection of specific IgE in allergy, its potential role in cancer has been investigated and prompted the definition of the field of AllergoOncology.[1] Most recent developments are collected in a position paper by the European Academy of Allergy and Clinical Immunology.[2]

IgE AND CANCER

IgE is an antibody with properties distinct from those of other isotypes, specifically in terms of its affinity for its cognate Fc receptor FcεRI. FcεRI-IgE immune complex formation can activate potent effector cells normally associated with acute and chronic allergic responses. IgE effector cells, such as eosinophils, mast cells, and macrophages, are also known to infiltrate tumors; tumor-associated tissue eosinophilia (TATE) or tumor-associated macrophages (TAMs, which can constitute up to 50% of a tumor mass and can be alternatively activated, M2) are characteristics of tumor inflammation. While intratumoral or stromal mast cells have been correlated with tumor promotion, signs of mast cell degranulation, normally associated with IgE–immune complex formation, have been correlated with a more favorable prognosis. Mast cells are a prominent source of the proinflammatory cytokine TNF-α, which is known to promote antitumor immunity. Other released mediators turn on acute (histamine) or chronic (eg, slow-reacting substance of anaphylaxis and cytokines) inflammation and promote amplification of innate effector mechanisms. These cells can harbor cytotoxic and phagocytic potential, which could be directed against tumors.

The potential efficacy of IgE antibodies engineered to recognize tumor antigens is exemplified *in vitro* by using cell-based assays, suggesting that IgE directed against tumor antigens engenders antibody-dependent cell-mediated cytotoxicity (ADCC) by human monocytes, whereas, through its interaction with FcγRs, IgG_1 of the same antigen specificity can instruct the same cells to trigger antibody-dependent cell-mediated phagocytosis (ADCP). IgE anti-cancer antibodies engage subsets of FcεRI-expressing effector cells to mediate ADCC against tumors without the inhibitory Fc receptor signals known to limit IgG effector functions in the tumor microenvironment. IgE is cross-linked by densely packed tumor antigens but not by soluble monovalent antigens, forming tumor-associated molecular patterns (TAMPs) on a cancer cell surface and therefore triggering effector cell activation at sites where antitumor immunity is needed (Fig 1). Therefore it is tempting to speculate that IgE antibodies directed against tumor antigens can propagate alternative or complementary antitumor functions to those of clinically available IgG mAbs specific for tumor antigens, such as epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). Prompted by promising preclinical studies in numerous *in vivo* models of cancer and in nonhuman primates, the first clinical trial of an antitumor IgE antibody in patients with cancer is ongoing (NCT02546921).

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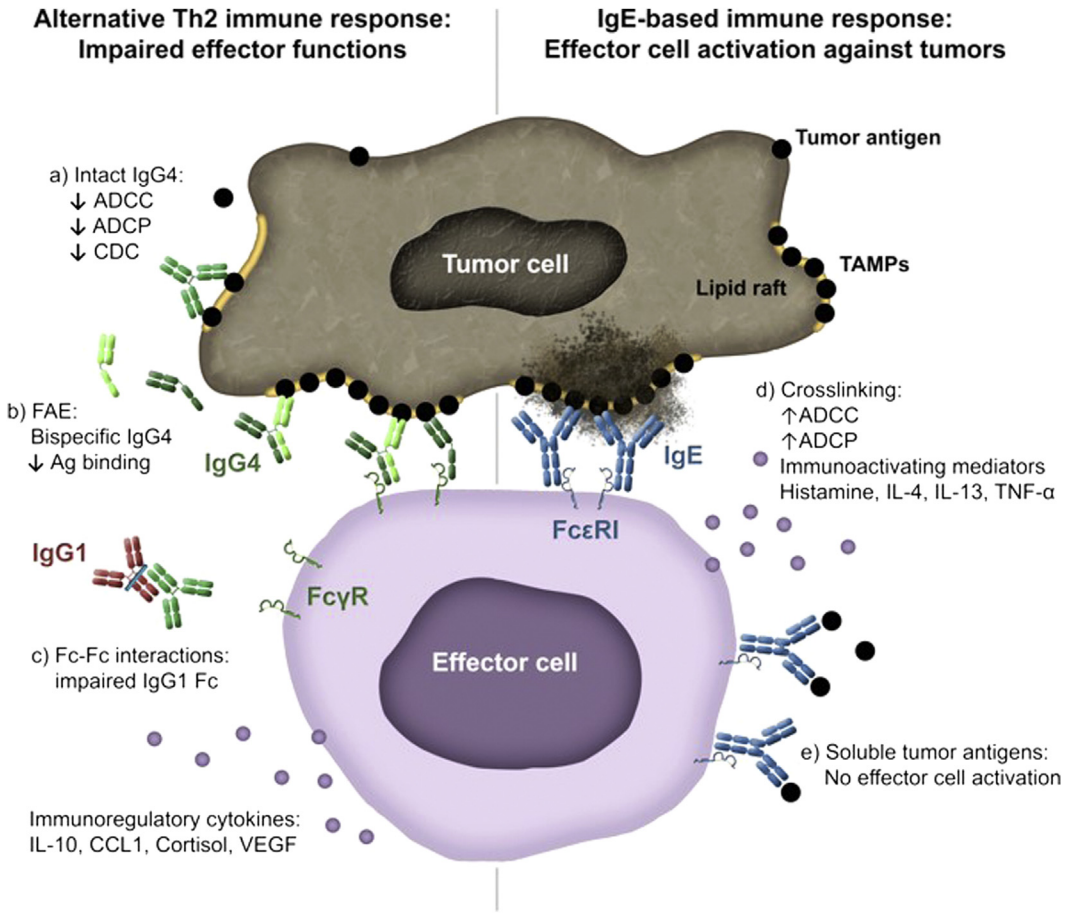

FIG 1. Antibody isotypes direct effector functions of innate immune cells infiltrating tumors. *Left,* Intratumoral IgG_4 supported by IL-10 and vascular endothelial growth factor *(VEGF)* produced by cancer and immune cells. IgG_4 occurs as intact IgG4 antibody *(a)*; can undergo Fab arm exchange *(FAE)*, resulting in bispecific or half antibodies *(b)*; or can interfere with IgG_1 Fc-mediated antitumor functions *(c)*. IgG_4 might be unable to cross-link FcγRs on effector cells and engender antitumor functions. *Right,* Tumor antigen-specific IgE is shuttled through $Fc\varepsilon RI^+$ effector cells into tumors. Overexpressed tumor antigens packed in lipid rafts assemble tumor-associated molecular patterns *(TAMPs)*, leading to effective cross-linking of effector cell-bound IgE, followed by antibody-dependent cellular cytotoxicity *(ADCC)* and antibody-dependent cellular phagocytosis *(ADCP)* of malignant cells *(d)*; soluble monovalent tumor antigens do not lead to effector cell activation *(e)*. *Ag,* Antigen; *CDC,* complement dependent cytotoxicity.

FROM T_H2 IMMUNE RESPONSES IN PATIENTS WITH ALLERGY AND ATOPY TO CANCER EPIDEMIOLOGY

Allergy is characterized by T_H2-dominant immune responses, featuring IL-4, IL-13, and thymic stromal lymphopoietin upregulation. Because these mediators can be observed in cancer tissues, strategies to activate these responses could in principle promote isotype switching to antitumor IgE and also IgE/FcεRI-associated cross-presentation by dendritic cells, resulting in activation of $CD4^+$ T cells but also of $CD8^+$ cytotoxic T lymphocytes. Therefore although T_H1 responses and a strong branch of $CD8^+$ cytotoxic T lymphocytes are generally desired in oncology, activation of classical T_H2 cells has also been associated with improved survival. On the other hand, TATE and TAMs, especially those alternatively activated M2 populations, might be signs of a T_H2-biased immune response unable to restrict cancer growth. Evidence of an alternative T_H2 inflammatory milieu featuring enhanced IL-10 rather than IL-4 in patients with many cancers, including melanoma, can influence class-switching away from IgE and perhaps favor expression of isotypes with more restricted effector functions, such as IgG_4 or IgA.

Therefore the question remains whether allergies in general can protect against cancer. Epidemiologic meta-analyses suggest a strong inverse association between allergy and atopy and risk of glioma, pancreatic cancer, and childhood leukemia, although there are limitations in previous studies related to measures of allergy history and latency period.[3] Inverse associations of prediagnostic IgE and cancer risk have also been reported overall, as well as for glioma specifically,[4,5] but fewer associations have been reported at other cancer sites.[2] Prospective studies in large cohorts are required to further understand the potential role of IgE and other immunologic parameters in cancer risk and potential underlying biological mechanisms to be able to better harness "classical" T_H2 immune responses and IgE against cancer.

IMMUNE TOLERANCE: GOOD OR BAD?

Immunotherapy strategies in oncology are hampered by an overwhelming immunosuppressive microenvironment in and

around tumors. Tumor cells and infiltrating immune cells, such as regulatory T cells and likely regulatory B cells,[6] can secrete cytokines, such as TGF-β and IL-10, which support immune tolerance[7] and moderate immune surveillance, hindering any antitumor activities of effector cells. Checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) to unleash the cytotoxic potential of a patient's T-cell immunity are major breakthroughs in clinical oncology, even at the cost of severe systemic autoimmunity.

In contrast, allergen immunotherapy attempts to re-establish immune tolerance to the allergen. A hallmark of allergen immunotherapy is IgG_4, which is supported by IL-10–producing cells, such as regulatory T and regulatory B cells. IgG_4 antibodies can block allergic responses through various mechanisms, such as through interacting with the inhibitory FcγRIIb on B cells to block IgE synthesis.[8] IgG_4 is also a special antibody isotype devoid of complement activation properties and with impaired effector functions. These characteristics might be due to hinge region sequences that render IgG_4 prone to Fab arm exchange and formation of naturally bispecific antibodies less able to be cross-linked by an allergen[9] and therefore resistant to allergen-associated molecular patterns (AAMPs) (Fig 1).[10] Furthermore, IgG_4 might repolarize M2a macrophages to the immunosuppressive phenotype M2b, which could be responsible for increased IL-10 secretion.[11] Strikingly, IgG_4 is expressed in tissues from patients with malignancies such as melanoma, in whom it can impair antitumor immunity and correlates with shorter survival and disease progression.[12] There is also increasing evidence to support positive correlations between IgG_4-related diseases, such as sclerosing cholangitis associated with autoimmune pancreatitis, with enhanced cancer risk,[13] including more recent long-term follow-up investigations.[14] However, the antigen specificities of IgG_4 antibodies are unclear.[15] Notably, higher levels of IgE and IgG_4 recognizing the cancer antigens EGFR and HER2, but not carcinoembryonic antigen, were detected in the sera of patients with cancer compared with allergic patients.[16] Therefore the tumor microenvironment could favor class-switching to IgG_4[17] within a "modified T_H2 response" in a process that features high similarities to those reported in patients with cat allergy.[18] Elucidating the conditions promoting IgG_4 isotype switching still requires the design of immunologically relevant animal models other than rodents, potentially monkeys or canines.[2]

Hence the opposite from allergen immunotherapy might be required in cancer treatment, ie, reduction of "alternative" T_H2 isotypes, such as IgG_4, *in situ* and simultaneous promotion of immune activatory IgE isotypes against cancer antigens. It might be envisaged that cancer immunotherapy strategies could aim at shifting existing IgG_4 responses to IgE through sequential isotype switching, perhaps with the aid of adjuvants.

CONCLUSION

Harnessing components of the "classical" T_H2 humoral immunity against tumors might offer novel oncological treatment avenues. Thus AllergoOncology might provide strategies that complement existing and emerging immuno-oncology therapies.

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